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Amyloid, cerebrovascular disease, and neurodegeneration biomarkers are associated with cognitive trajectories in a racially and ethnically diverse, community-based sample

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ABSTRACT

We characterized the additive contribution of cerebrovascular biomarkers to amyloid and neurodegeneration biomarkers (AV(N)) when modeling prospective, longitudinal cognitive trajectories within 3 major racial/ethnic groups. Participants (n = 172; age = 69–96 years; 62% women; 31%/49%/20% Non–Hispanic White/Non–Hispanic Black/Hispanic) from the Washington Heights-Inwood Columbia Aging Project were assessed for amyloid (Florbetaben PET), neurodegeneration (cortical thickness, hippocampal volume), and cerebrovascular disease (white matter hyperintensity (WMH), infarcts). Neuropsychological assessments occurred every 2.3 ± 0.6 years for up to 6 visits (follow-up time: 4.2 ± 3.2 years). Linear mixed-effects models were stratified by race/ethnicity groups. Higher amyloid was associated with faster memory decline in all 3 racial/ethnic groups, but was related to faster cognitive decline beyond memory in minoritized racial/ethnic groups. Higher WMH was associated with faster language, processing speed/executive function, and visuospatial ability decline in Non–Hispanic Black participants, while infarcts were associated with faster processing speed/executive function decline in Non–Hispanic White participants. Complementary information from AD, neurodegenerative, and cerebrovascular biomarkers explain decline in multiple cognitive domains, which may differ within each racial/ethnic group. Importantly, treatment strategies exist to minimize vascular contributions to cognitive decline.

Introduction

The National Institute on Aging and the Alzheimer's Association (NIA-AA) established a research framework for Alzheimer's disease (AD) that uses amyloid, tau, and neurodegeneration to describe disease progression and a separate cognitive staging scheme to describe disease severity (Jack et al., 2018). The guidelines explicitly mention that studies can interrogate AD without measures of all 3 biomarkers and can incorporate additional contributing factors, such as cerebrovascular disease. Alzheimer's disease and cerebrovascular disease pathology can both lead to neurodegeneration, the pathologic change most proximal to symptom onset and progression in AD (Jack et al., 2018; Rizvi et al., 2021; Rizvi et al., 2018). Beyond converging on neurodegeneration and cognitive impairment, cerebrovascular disease may have a mechanistic relationship with tau (Laing et al., 2020), but not amyloid (Lao and Brickman, 2018; Roseborough et al., 2017).

Minoritized racial/ethnic groups in community-based studies have elevated markers of cerebrovascular disease, particularly white matter hyperintensity (WMH) volume (Brickman et al., 2008; Nyquist et al., 2014), and a higher age-adjusted incidence rate of AD compared with Non–Hispanic White adults (Tang et al., 2001). Our investigation of race/ethnicity is not from a genetic perspective, but rather from the perspective of interlocking structural

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forces that create and maintain conditions that lead to health disparities (Adler and Newman, 2002; Risch et al., 2002). There are several frameworks (Crenshaw, 1990; Forde et al., 2019; Hill et al., 2015; Meyer et al., 2008) through which to consider how social determinants of health affect biology and clinically-relevant outcomes from multiple pathways (i.e., socioeconomic disadvantage (Geronimus, 1992), discrimination and stress (Williams and Mohammed, 2009), allostatic load (Beckie, 2012)). Characterizing the contribution of cerebrovascular disease, for which effective treatments exist, to AD, for which effective treatments do not yet exist, may identify a pharmacologic therapeutic strategy, in tandem with socially equitable policies that promote positive social determinants of health, to close the racial and/or ethnic disparity in AD (Power et al., 2021).

We explored the association of amyloid, cerebrovascular disease, and neurodegeneration with cognitive trajectories in diverse, community-dwelling older adults. We anticiapted (1) that greater amyloid and neurodegeneration would be associated with faster cognitive decline over time, and (2) that cerebrovascular disease would be more prevalent in minoritized racial/ethnic groups and contribute to cognitive decline when present.

Materials and methods

Participants

Participants were enrolled in the Washington Heights Inwood Columbia Aging Project (WHICAP) (Manly et al., 2005; Tang et al., 2001). Briefly, Medicare eligible individuals were recruited from the community surrounding Columbia University Medical Center. Study visits include the collection of medical, neurologic, neuropsychological, and functional data (Manly et al., 2005; Tang et al., 2001). Participants self-identified as Non–Hispanic White, Non–Hispanic Black, or Hispanic using the format of the 2000 US Census (Bureau, 1991). The term "sex/gender" is used due to insufficient information in the questionnaire such that the two constructs could not be separated. Apolipoprotein epsilon (*APOE*) genotyping was performed and coded as *APOE ε4* non–carrier or *APOE ε4* carrier (i.e., having at least 1 *APOE ε4* allele). Medical history of hypertension, diabetes mellitus, and heart disease (i.e., atrial fibrillation and other arrhythmias, myocardial infarction, congestive heart failure, or angina pectoris) were self-reported. A subset (n = 172) underwent one timepoint of amyloid PET scanning, structural T1-weighted and T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI scanning, as well as longitudinal comprehensive neuropsychological assessments (Non–Hispanic White: 12 with 1 visit, 17 with 2 visits, 11 with 3 visits, 11 with 4 visits, 2 with 5 visits, follow-up time: 3.6 ± 2.8 years; Non–Hispanic Black: 23 with 1 visit, 19 with 2 visits, 25 with 3 visits, 13 with 4 visits, 4 with 5 visits, follow-up time: 3.8 ± 3.1 years; Hispanic: 2 with 1 visit, 6 with 2 visits, 8 with 3 visits, 12 with 4 visits, 4 with 5 visits, 3 with 6 visits, follow-up time: 6.1 ± 3.2 years). Variable number of follow-up visits was a result of differences in enrollment phases. The imaging visit was anchored as "baseline" and all subsequent visits for neuropsychological assessment were included. The length of time in the study prior to the "baseline" imaging visit did not differ among race/ethnicity groups ($F[2] = 0.35$, $p = 0.71$). All participants provided informed consent according to the Declaration of Helsinki and study procedures were approved by the local Institutional Review Board.

PET and MRI scanning

Participants underwent amyloid PET imaging with an 8.1 mCi target dose of [^{18}F]Florbetaben in a Siemens Biograph mCT scanner (iterative reconstruction, 5-minute frames, voxel size: 1.59 × 1.59 × 3mm^3). The standard uptake value ratio (SUVR) was calculated using data 50–70 minutes post-injection and an inferior cerebellar gray matter reference region in native space. A global composite was calculated as an average of SUVRs in Thal phase (Thal et al., 2002) regions including frontal cortex, temporal cortex, parietal cortex, cingulate cortex, and striatum, defined using FreeSurfer regions of interest. For comparison to other cohorts, an amyloid positivity cutoff of 1.25 SUVR (i.e., 2 standard deviations above the mean of the lower Gaussian when a 2 Gaussian distribution was fit to the sample distribution) was used to determine the frequency of amyloid positivity.

T2-weighted MRI was also collected in a 1.5T Philips Intera scanner or a 3T Philips Achieva scanner using comparable FLAIR sequences (repetition time (TR)/echo time (TE)/inversion time (TI): 5500/144/1900 ms, flip angle: 90°, voxel size: 0.98 × 0.98 × 3.0 mm^3; TR/TE/TI: 8000/332/2400 ms, flip angle: 50°, voxel size: 1.1 × 1.1 × 0.6 mm^3, respectively). T2-weighted images were processed with in-house software to segment hyperintense voxels as WMH, representing ischemic small vessel cerebrovascular disease. Briefly, this pipeline involved extracting the brain, thresholding each image at 2.1 standard deviations above the mean voxel intensity per slice, and labeling clusters larger than 5 contiguous voxels as WMH. Final WMH images were visually inspected for accuracy and manually edited if necessary. Total WMH was summed across frontal, temporal, parietal, and occipital lobes (Admiraal-Behloul et al., 2004) as one vascular (V) biomarker. Due to the skewed distribution, WMH volumes were log-transformed. Infarcts represent large vessel cerebrovascular disease and were identified on T2-weighted as MRI discrete hypointense lesions larger than 5 mm with a partial or complete hyperintense ring, with confirmation on T1-weighted MRI as areas of hypointensity. Visual read was performed by an expert rater (JG). Out of the 85 of 172 (49%) with at least 1 infarct, 72 of 85 (85%) had only 1. Due to the highly skewed distribution, infarcts were dichotomized as absent or present as another vascular (V) biomarker.

Structural T1-weighted MR imaging was performed in a 1.5T Philips Intera scanner or a 3T Philips Achieva scanner using comparable magnetization prepared rapid acquisition gradient echo (MPRAGE) sequences (TR/TE: 20/2.1 ms, flip angle: 20°, voxel size: 0.94 × 0.94 × 1.3 mm^3; TR/TE: 6.5/3.0 ms, flip angle: 8°, voxel size: 1 × 1 × 1 mm^3, respectively), depending on participant enrollment in the study. T1 images were anatomically segmented with FreeSurfer v5.1 with manual supervision (Dale et al., 1999). Cortical thickness in AD signature regions (Dickerson et al., 2011) was calculated for FreeSurfer-defined rostral medial temporal pole, angular gyrus, inferior frontal lobe, inferior temporal lobe, temporal pole, precuneus, supramarginal gyrus, superior parietal lobe, superior frontal lobe, medial temporal lobe, and posterior cingulate as one neurodegenerative ((N)) biomarker. FreeSurfer-defined hippocampal volume as a percentage of FreeSurfer-defined intracranial total volume was used as another neurodegenerative ((N)) biomarker.

These analyses combined biomarker levels from 1.5T and 3T MRI scanners using the same WMH and FreeSurfer segmentation pipelines, and the same criteria for visual read of infarcts. There were no systematic differences in biomarker values by scanner.

Neuropsychological assessment

All participants were evaluated with a neuropsychological battery to assess a broad range of cognitive function, including memory, language, processing speed/executive function, visuospatial ability. The battery included widely used standardized neuropsychological tests (Stern et al., 1992), and was conducted in English

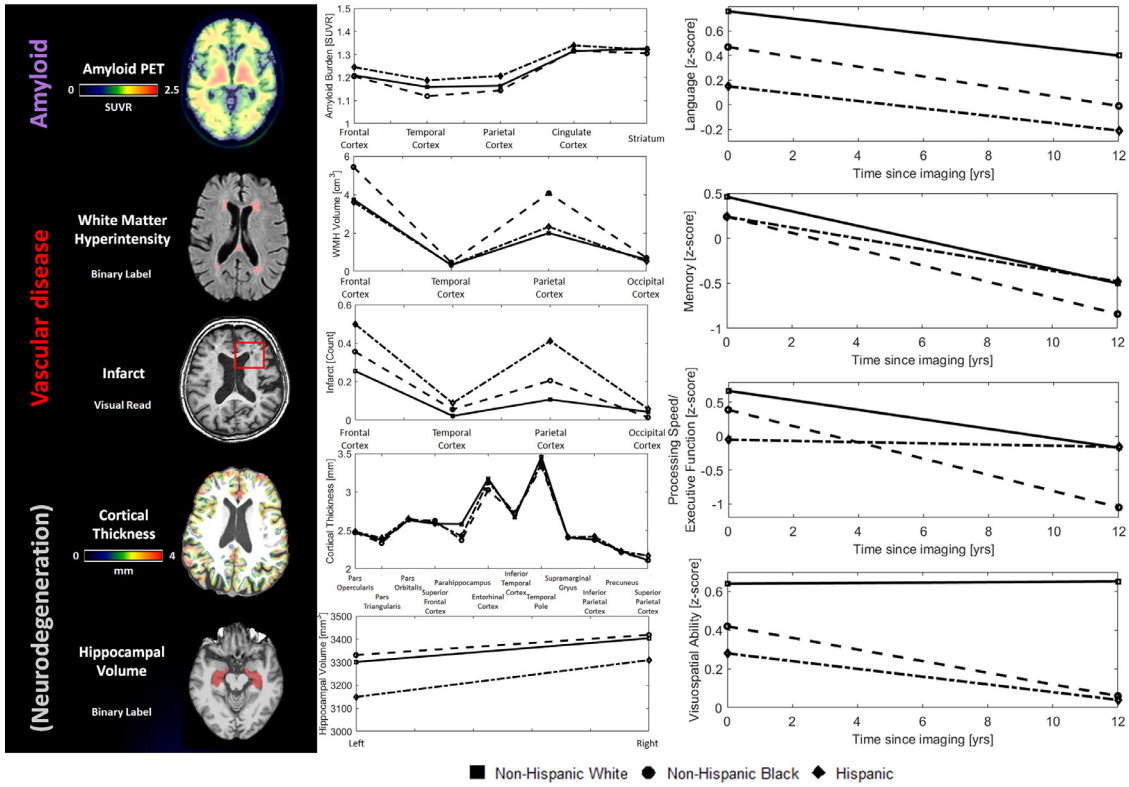

Fig. 1. (Left) Representative images of amyloid, neurodegeneration, and cerebrovascular biomarkers. (Middle) Race/ethnicity group averages at each region of interest, highlighting regional patterns across groups. (Right) Race/ethnicity group average trajectories in 4 cognitive domains.

or Spanish by bilingual research staff (participants were asked their opinion of which language would yield their best performance at study entry, and this language was used throughout all follow-up visits). Summary scores were created for language, memory, processing speed/executive function, and visuospatial ability through confirmatory factor analysis, and were found to be time-, language-, and education-invariant as well as being configurally invariant across AD diagnosis (Avila et al., 2020b; Siedlecki et al., 2008; Siedlecki et al., 2010). Briefly, summary scores were derived by averaging z-scores from 15 neuropsychological tests in 4 respective domains. Z-scores were computed based on the means and standard deviations of test performance by participants without dementia in the first wave of WHICAP participants in 1992. Summary scores for all domains were approximately normally distributed within each racial/ethnic group, and racial/ethnic differences were present at study entry and "baseline" imaging visit. At the time of imaging, there were prevalent diagnoses of MCI (n = 24; 10 Non–Hispanic White; 9 Non–Hispanic Black; 5 Hispanic) or AD (n = 9; 1 Non–Hispanic White; 5 Non–Hispanic Black; 3 Hispanic), following previously described consensus diagnosis and following standard research criteria (Association, 2013; Manly et al., 2005; McKhann et al., 2011).

Statistical analysis

Table 1 summarizes demographic data, vascular risk factors, AV(N) biomarker levels, and cognitive data by racial/ethnic group. Fig. 1 shows a representative scan for each AV(N) biomarker, their distribution across regions included in each composite measure, and the unconditional growth curves. We summarized the demographic variables of those with PET imaging (n = 172) and compared them to the larger WHICAP cohort across all 3 recruitment waves (N = 5923) to compute inverse probability weights to reduce potential selection bias. The Non–Hispanic White group who underwent PET imaging was younger by 4.5 years ([2.5, 6.4], p = 7E–6), had more years of formal education by 1.4 years ([0.34, 2.4], p = 0.009), and were more likely to be men ($\chi 2$ [1] = 4.6, p = 0.03; imaging: 53% men/47% women vs. non–imaging: 38%/62%) than those who did not undergo PET imaging. The Non–Hispanic Black group who underwent PET imaging was younger by 3.3 years ([1.7, 4.8], p = 3.2E–5) and had more years of formal education by 1.6 years ([0.7, 2.4], p = 3E–4) than those who did not undergo PET imaging, but there was no difference by sex/gender distribution ($\chi 2$[1] = 1.9E–4, p = 0.99). The Hispanic group who underwent PET imaging was younger by 3.6 years ([1.4, 5.8], p = 0.001) and had more years of formal education by 1.7 years ([0.18, 3.2], p = 0.03) than those who did not undergo PET imaging, but there was no difference by sex/gender distribution ($\chi 2$ [1] = 0.19, p = 0.66). Inverse probability weights adjusted for the younger age and greater number of years of education in the PET imaging subsample such that biomarker effects on cognitive trajectories more appropriately reflect the community-based sample by up-weighting participants (i.e., entering them multiple times into the model) who are demographically similar to those without PET imaging and down-weighting participants who are not demographically similar to those without PET imaging (Mansournia and Altman, 2016; van der Wal and Geskus, 2011).

A series of models informed by the amyloid-tau-neurodegeneration (AT(N)) framework was used; we lacked a tau (T) biomarker, and additionally included vascular (V) biomarkers. Growth curves were assessed with linear and quadratic time terms; model fit for all domains for all groups was best when considering time as a linear term. We used a series of linear mixed effects models (random subject level intercept and slope over time, and covariance between the 2), stratified by race/ethnicity, to estimate the associations between base-

Table 1
Demographic variables, vascular risk factors, biomarkers of amyloid, white matter hyperintensity (WMH) volume, presence of infarcts (none vs. at least 1), cortical thickness, and hippocampal volume (relative to intracranial total volume), and factor scores of memory, language, processing speed/executive function, and visuospatial ability for the PET imaging subset of WHICAP.

	Total	Non-Hispanic White	Non-Hispanic Black	Hispanic	Test statistic, p-value
N (%)	172 (100%)	53 (30.8%)	84 (48.8%)	35 (20.3%)	-
Age [yrs]	81.0 ± 6.0	80.4 ± 5.6	81.4 ± 6.3	81.0 ± 5.8	F(2) = 0.47, p = 0.63
Sex/Gender [N (%) women]	107 (62.2%)	25 (47.2%)	59 (70.2%)	23 (65.7%)	$\chi^2(2) = 7.6$, p = 0.02
Education	13 ± 4	15 ± 3	13 ± 3	8 ± 4	F(2) = 35.4, p = 1.5E-13
APOE ε4 [N (%) carrier]	55 (32.4%)	17 (32.7%)	30 (36.1%)	8 (22.9%)	$\chi^2(2) = 2.0$, p = 0.37
Hypertension [N (%) present]	135 (88.2%)	39 (83.0%)	65 (90.3%)	31 (91.2%)	$\chi^2(2) = 1.8$, p=0.40
Diabetes Mellitus [N (%) untreated] [N (%) treated]	5 (3.3%) 28 (18.3%)	0 (0%) 7 (14.9%)	3 (4.2%) 14 (19.4%)	2 (5.9%) 7 (20.6%)	$\chi^2(4) = 3.3$, p=0.51
Heart Disease [N (%) untreated] [N (%) treated]	19 (12.4%) 35 (22.8%)	5 (10.6%) 14 (29.8%)	13 (18.1%) 10 (13.9%)	1 (2.9%) 11 (32.4%)	$\chi^2(4) = 9.6$, p=0.048
Amyloid SUVR	1.24 ± 0.23	1.24 ± 0.21	1.23 ± 0.23	1.26 ± 0.26	F(2) = 0.13, p = 0.88
WMH volume [cm^3]	8.44 ± 10.7	6.25 ± 8.31	10.8 ± 12.4	6.09 ± 8.05	F(2) = 5.0, p = 0.008
Infarct [N (%)]	84 (48.8%)	22 (41.5%)	45 (53.6%)	17 (48.6%)	$\chi^2(2) = 1.9$, p = 0.39
Cortical Thickness in AD signature [mm]	2.58 ± 0.12	2.61 ± 0.12	2.56 ± 0.12	2.59 ± 0.11	F(2) = 3.8, p = 0.02
Hippocampal Volume normalized to Intracranial Total Volume [%]	0.37 ± 0.12	0.37 ± 0.12	0.37 ± 0.12	0.37 ± 0.13	F(2) = 0.03, p = 0.97
Lag time [yrs]	0.56 ± 0.44	0.56 ± 0.33	0.57 ± 0.47	0.53 ± 0.49	F(2) = 0.12, p = 0.88
Language [z-score]	0.49 ± 0.58	0.79 ± 0.54	0.46 ± 0.53	0.12 ± 0.54	F(2) = 16.9, p = 2.1E-7
Memory [z-score]	0.32 ± 0.74	0.51 ± 0.63	0.24 ± 0.77	0.23 ± 0.78	F(2) = 2.4, p = 0.09
Processing Speed/ Executive Function [z-score]	0.39 ± 0.99	0.68 ± 0.76	0.35 ± 1.1	0.06 ± 1.0	F(2) = 4.0, p = 0.02
Visuospatial ability [z-score]	0.45 ± 0.51	0.65 ± 0.41	0.42 ± 0.47	0.23 ± 0.66	F(2) = 7.9, p = 0.001

Abbreviations: APOE ε4 = apolipoprotein epsilon 4 allele; AD = Alzheimer's disease; SUVR = standard uptake value ratio; WMH = white matter hyperintensity; Lag time between MRI/PET scan and neuropsychological assessment.
Note: n=153 for hypertension, diabetes mellitus, and heart disease.

line imaging biomarkers and longitudinal cognitive outcomes: a demographically-adjusted model that included age, sex/gender, education, and *APOE ε4*, and a model that additionally included amyloid, WMH volume or presence of infarct, and cortical thickness or hippocampal volume (AV(N) model). We report a range of *p*-values for a single biomarker, taken from the various models, including amyloid-WMH-cortical thickness, amyloid-infarct-cortical thickness, amyloid-WMH-hippocampal volume, and amyloid-infarct-hippocampal volume biomarkers.

We had several reasons to stratify models by race/ethnicity. Our characterization focuses on the effects present within each group, rather than comparing minoritized groups to a "reference" group. We aim to communicate our findings in a participant-centered manner that does not further stigma. Conceptually, this approach allowed covariates like age, sex/gender, education, and *APOE ε4* to operate differently in each group due to factors such as weathering (Forde et al., 2019), intersectionality (Avila et al., 2020a), historical differences in educational quality (Vonk et al., 2019), and previous evidence that *APOE ε4* has a smaller impact on outcomes despite being more prevalent in Non–Hispanic Black participants (Barnes et al., 2013; Turney et al., 2020) without seven 3-way interactions (e.g., time x baseline age x race/ethnicity). Further, the amount of between-subject variability in cognitive trajectory (i.e., random subject level intercepts and slopes, and the covariance between the two) was allowed to differ between racial/ethnic groups by fitting stratified models, accounting for the different levels of heterogeneity in each racial/ethnic group. Finally, group-mean centering all continuous variables allowed for direct interpretation at meaningful values as opposed to grand-mean centering (e.g., the grand mean of 13 years of education is not appropriate in our sample of Hispanic participants with a group mean of 8 years of education). These issues are most simplistically addressed in our stratification approach, and the smaller sample size within each racial/ethnic group are offset by the amount of longitudinal data (Wiley and Rapp, 2019). All statistical analyses were considered significant at $p < 0.05$ and discussed up to $p < 0.10$. Reporting descriptive results up to $p < 0.10$ is important when considering biological mechanisms that have been observed previously in

large, highly selected samples within relatively small, but representative community-based samples to ensure that plausible mechanisms are not overlooked. All statistics were run in R 3.6.1.

Data availability

Data from the WHICAP study are available upon data request, pending approval by study investigators (https://www.cumc.columbia.edu/adrc/investigators).

Results

Baseline differences by race and/or ethnicity

Participants were 69–96 years old, mostly women, mostly Non–Hispanic Black, and had 0–20 years of education. The percentage of women differed across race/ethnicity (Non–Hispanic Black, Hispanic > Non–Hispanic White; Table 1). Educational attainment differed across race/ethnicity (Non–Hispanic White > Non–Hispanic Black > Hispanic; Table 1). In the PET subsample, hypertension and diabetes mellitus were not different by race/ethnicity, but heart disease was more often untreated in the Non–Hispanic Black group compared to the other two groups (Table 1). Fig. 1 shows the image-based biomarkers for amyloid, WMH volume, presence of infarcts, cortical thickness, and hippocampal volume, and their regional distribution by racial/ethnic group. Supplemental Fig. 1A shows the individual variability within each racial/ethnic group. Amyloid SUVR was similar across groups (n = 62 (36%) amyloid positivity in all participants; n = 21 (40%) in Non–Hispanic White group; n = 26 (31%) in Non–Hispanic Black group; n = 14 (40%) in Hispanic group), WMH volume was greatest in Non–Hispanic Black participants, the proportion of individuals with infarcts was similar across groups, cortical thickness was greatest in Non–Hispanic White participants, and relative hippocampal volume was similar across groups (Table 1). Baseline cognitive performance in language, memory, processing speed/executive function, and visuospatial ability were all greatest in Non–Hispanic White participants (Table 1). Baseline associations among amyloid, neurodegeneration, and cerebrovascular disease biomarkers and cognitive performance after adjustment for age, sex/gender, education, and *APOE ε4* allele are shown for each racial/ethnic group in Supplemental Fig. 2. The major deviations from expected associations were higher cortical thickness in Non–Hispanic Black participants with infarcts and higher hippocampal volume with higher WMH volume in Hispanic participants.

Cognitive trajectories in demographically-adjusted models by race and/or ethnicity

Unconditional linear growth curves (i.e., not adjusted for covariates) are shown for each racial/ethnic group in Fig. 1, and for individuals within each racial/ethnic group (i.e., random subject level variability) in Supplemental Fig. 1B. By stratifying the models by race/ethnicity, the variances were not constrained to be equal across racial/ethnic groups. Conditional growth curves (Table 2) showed that in Non–Hispanic White participants, faster language decline was associated with older age and observed in women compared to men; faster memory decline was associated with older age and fewer years of education; faster processing speed/executive function decline was associated with having an *APOE ε4* allele; and visuospatial ability decline was not associated with any covariates. In Non–Hispanic Black participants, faster language decline was associated with older age; memory decline was not associated with any covariates; faster processing speed/executive function decline was associated with older age; and visuospatial ability decline was not associated with any covariates. In Hispanic participants, language, memory, processing speed/executive function, and visuospatial ability declines were not associated with any covariates.

Cognitive trajectories in AV(N) models by race and/or ethnicity

Plots of adjusted amyloid-WMH-cortical thickness models are shown in Fig. 2, while numerical values from all AV(N) models are presented in Tables 3-6. Faster language decline was associated with higher amyloid (B = -0.07, $p = 0.05$) and higher WMH (B = -0.04, $p = 0.01$) in Non–Hispanic Black participants (Table 3), and with higher amyloid (B = -0.15 to -0.15, $p = 0.03$–0.04) in Hispanic participants (Tables 3-6). However, the association between language decline and amyloid in Non–Hispanic Black participants was not robust to different model specifications that included infarcts rather than WMH or that included hippocampal volume rather than cortical thickness (Tables 4-6). Faster memory decline was associated with higher amyloid in Non–Hispanic White participants (B = -0.3 to -0.23, $p = 0.01$–0.03; Tables 3-6), but with lower WMH (B = 0.09–0.09, $p = 0.05$–0.05; Tables 3 and 5) in Hispanic participants. Faster processing speed/executive function decline was associated with the presence of infarcts in Non–Hispanic White participants (B = -0.09 to -0.09, $p = 0.04$–0.04; Tables 4 and 6), and with higher WMH (B = -0.11 to -0.10, $p = 0.01$–0.05; Tables 3 and 5) but higher cortical thickness (B = -0.72 to -0.63, p = 3E–4 to 5E–3; Tables 3-4) in Non–Hispanic Black participants. Faster visuospatial ability decline was associated with higher WMH in Non–Hispanic Black participants (B = -0.05 to -0.05, p = 5E–3 to 6E–3; Tables 3 and 5) and with higher amyloid in Hispanic participants (B = -0.18 to -0.18, $p = 0.05$–0.05; Tables 5-6). However, the association between visuospatial ability decline and amyloid in Hispanic participants was not robust to different model specifications including cortical thickness rather than hippocampal volume (Tables 3-4).

Descriptively, it is important to point out associations within the AV(N) framework that may be operating in our relatively small, but representative community-based sample given the current vascular cognitive impairment and dementia (VCID) and AD literature. Faster language decline appeared to be related to lower hippocampal volume in Non–Hispanic Black participants (B = 0.13–0.14, p = 0.09–0.12; Tables 5-6). Faster memory decline appeared to be related to higher amyloid (B = -0.10 to -0.08, p = 0.09–0.21; Tables 3-6) and higher WMH (B = -0.05 to -0.04, p = 0.08–0.09; Tables 3 and 5) in Non–Hispanic Black participants, and appeared to be related to higher amyloid (B = -0.16 to -0.15, p = 0.06–0.10; Tables 3-6) in Hispanic participants.

Discussion

We characterized patterns of multiple domain cognitive decline within three racial/ethnic groups represented in a community-based study using a comprehensive biomarker profile including cerebrovascular biomarkers that contribute to cognitive decline, when present, and are often more present in minoritized groups due to social determinants of health. There were three main findings of our study. First, higher amyloid was associated with faster memory decline in all participants, above and beyond biomarkers of neurodegeneration and cerebrovascular disease. Second, amyloid-related cognitive decline was limited to memory in Non–Hispanic White participants, while amyloid-related cognitive decline was further observed for language in Non–Hispanic Black participants and for language and visuospatial ability in Hispanic participants. Third, when biomarkers of cerebrovascular disease were present, indicators of worse vascular injury were associated with

Table 2
Association parameters for the conditional growth curve model in each racial/ethnic group, focusing on slope parameters. Example model specification is as follows: Cognitive performance over time ~ intercept + time + age + sex/gender + education + *APOE ε4* + age X time + sex/gender X time + education X time + *APOE ε4* X time.

Conditional Growth Curve		Within Race/Ethnicity		
		Non-Hispanic White	Non-Hispanic Black	Hispanic
Language	Time	4E-3 [-0.02,0.03] p=0.75	-0.04 [-0.08,-0.01] p=0.01	-0.03 [-0.08,0.03] p=0.35
	Baseline Age x Time	-8E-3 [-0.01,-4E-3] p=6E-5	-3E-3 [-6E-3,-4E-4] p=0.03	-3E-3 [-9E-3,4E-3] p=0.45
	Sex/Gender x Time	-0.04 [-0.07,-4E-3] p=0.03	2E-3 [-0.03,0.04] p=0.91	4E-3 [-0.06,0.07] p=0.9
	Education x Time	-2E-3 [-9E-3,5E-3] p=0.53	-1E-3 [-6E-3,3E-3] p=0.59	2E-3 [-5E-3,1E-2] p=0.56
	APOE ε4 x Time	-0.04 [-0.08,2E-3] p=0.07	0.02 [-0.02,0.05] p=0.43	-0.04 [-0.12,0.04] p=0.33
Memory	Time	-0.04 [-0.11,0.02] p=0.18	-0.13 [-0.19,-0.07] p=1E-4	-0.04 [-0.11,0.03] p=0.29
	Baseline Age x Time	-9E-3 [-0.02,-1E-3] p=0.04	-4E-3 [-9E-3,1E-3] p=0.14	-1E-3 [-0.01,7E-3] p=0.75
	Sex/Gender x Time	-0.06 [-0.14,0.02] p=0.18	0.05 [-0.02,0.12] p=0.14	-0.02 [-0.11,0.07] p=0.65
	Education x Time	0.03 [8E-3,0.04] p=9E-3	3E-3 [-5E-3,0.01] p=0.47	4E-3 [-6E-3,0.01] p=0.44
	APOE ε4 x Time	-0.04 [-0.13,0.04] p=0.34	-2E-3 [-0.07,0.06] p=0.95	-0.02 [-0.12,0.09] p=0.73
Processing Speed/ Executive Function	Time	-0.03 [-0.1,0.04] p=0.39	-0.16 [-0.26,-0.07] p=2E-3	-0.02 [-0.1,0.06] p=0.71
	Baseline Age x Time	-9E-3 [-0.02,6E-4] p=0.08	-0.01 [-0.02,-6E-3] p=1E-3	-2E-4 [-0.01,0.01] p=0.97
	Sex/Gender x Time	9E-3 [-0.08,0.1] p=0.85	0.08 [-0.03,0.18] p=0.16	-0.01 [-0.11,0.09] p=0.82
	Education x Time	-1E-2 [-0.03,1E-2] p=0.34	-1E-2 [-0.02,4E-3] p=0.16	-6E-3 [-0.02,4E-3] p=0.23
	APOE ε4 x Time	-0.14 [-0.24,-0.04] p=0.01	-0.07 [-0.17,0.04] p=0.22	0.03 [-0.08,0.15] p=0.58
Visuospatial Ability	Time	-8E-3 [-0.05,0.04] p=0.71	-5E-3 [-0.05,0.04] p=0.81	-0.05 [-0.12,0.02] p=0.15
	Baseline Age x Time	-1E-3 [-7E-3,5E-3] p=0.69	-2E-3 [-5E-3,2E-3] p=0.33	-8E-3 [-0.02,1E-4] p=0.07
	Sex/Gender x Time	-8E-4 [-0.06,0.06] p=0.98	-0.02 [-0.07,0.02] p=0.32	0.05 [-0.04,0.13] p=0.28
	Education x Time	6E-3 [-5E-3,0.02] p=0.3	-1E-3 [-7E-3,5E-3] p=0.72	5E-3 [-5E-3,0.01] p=0.34
	APOE ε4 x Time	0.03 [-0.04,0.09] p=0.42	-0.03 [-0.07,0.02] p=0.26	-0.03 [-0.12,0.07] p=0.62

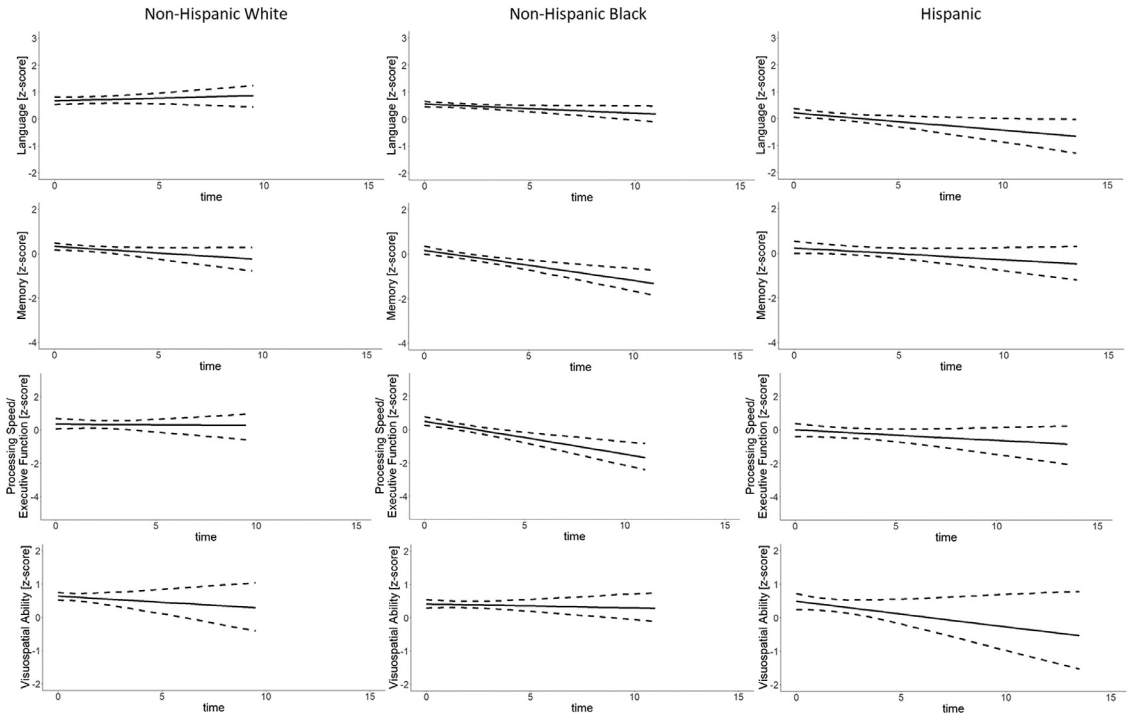

Fig. 2. Representative adjusted growth curves for the amyloid, white matter hyperintensity volume, and cortical thickness in each domain by race/ethnicity. 95% Confidence intervals visualize the effect of fewer participants at longer follow-up times.

faster decline; in Non–Hispanic White participants, infarcts were associated with faster processing speed/executive function decline and in Non–Hispanic Black participants, higher WMH was associated with faster language, processing speed/executive function, and visuospatial ability decline. Overall, comprehensive biomarker profiles explained subsequent cognitive decline in four major domains over time in a community-based, racially/ethnically diverse, older sample in which mixed pathology is common (Kapasi et al., 2017), especially in minoritized racial and/or ethnic groups (Barnes et al., 2015).

A research framework for AD (Jack et al., 2018) must evolve to identify the brain predictors of cognitive outcomes and clinical presentation beyond the variability that can be attributed to traditional AD biomarkers (i.e., ATX(N) (Hampel et al., 2021)). The primary focus of this study was on the added contribution of cerebrovascular disease to the AT(N) framework in different racial/ethnic groups, but more research is needed on other relevant factors (e.g., genetic, biological, environmental, social) that may affect biomarkers of disease, cognitive trajectories, and the relationship between the two within each racial/ethnic group. In this study, we did not include measures of racism, which has multiple levels (e.g., institutionalized, personally mediated, internalized (Jones, 2000)) that could affect the relationship between biomarkers and cognitive function (for a review on potential pathways from racism to health outcomes, see (Hill et al., 2015; Press, 2014)), but aim to interpret our findings in the context of these interlocking structural forces that differentially affect racial/ethnic groups.

First, we examined baseline differences in biomarker levels, cognitive performance, and social determinants of health by race/ethnicity groups. Discrimination based on race, ethnicity, language, and immigration status, among other group identities, may affect participant's overall health through a variety of mechanisms including life course accumulation of stress and biased opportunities and resource utilization (e.g., blood pressure lowering interventions were successful in community barbershop settings but not in traditional healthcare settings (Victor et al., 2018)). Heart conditions were more likely to be untreated in the Non–Hispanic Black participants, which may have manifested as greater WMH volume compared to the Non–Hispanic White and Hispanic participants. The number of years of formal education was lower in Non–Hispanic Black and Hispanic older adults, which may contribute to lower baseline scores on neuropsychological tests compared to Non–Hispanic White participants despite no group differences in amyloid or hippocampal volume. Strikingly, the distinction between greater amyloid and faster memory decline versus greater cerebrovascular disease and faster executive function/processing speed was observed in the Non–Hispanic White group, but not in the Non–Hispanic Black or Hispanic groups. Social factors may be driving greater convergence of cerebrovascular disease and AD pathophysiology in minoritized populations.

In this WHICAP PET subset, similar to what was reported in the larger WHICAP MRI subset, we observed no differences in amyloid, infarcts (Zahodne et al., 2015), or hippocampal volume (Brickman et al., 2008), but found that WMH volume was highest in Non–Hispanic Black participants (Brickman et al., 2008) and cortical thickness in AD signature regions was highest in Non–Hispanic White participants (Zahodne et al., 2015). Previous studies suggest lower (Deters et al., 2021) or higher (Gottesman et al., 2016) amyloid and lower (Morris et al., 2019) or similar levels (Meeker et al., 2021) of tau; greater neurodegeneration in AD-relevant regions (Meeker et al., 2021); and greater WMH volume (Meeker et al., 2021) in Non–Hispanic Black participants compared to Non–Hispanic White participants. Despite general convergence, slight discrepancies in studies could be attributable to measurement/acquisition differences, recruitment strategy differences, and/or race in place (i.e., racial/ethnic self-identification and/or treatment based on perceived race/ethnicity depend on place, time period, and context (Ford et al., 2010)). Continued studies with a focus on inclusion and representation can help untangle mixed findings and identify relevant social determinants of health as

Table 3
Association parameters for the AV(N) model including amyloid, white matter hyperintensity volume, and cortical thickness in each racial/ethnic group, focusing on slope parameters. Example model specification is as follows: Cognitive performance over time ~ intercept + time + age + sex/gender + education + *APOE ε4* + amyloid + cerebrovascular disease + neurodegeneration + age X time + sex/gender X time + education X time + *APOE ε4* X time + amyloid X time + cerebrovascular disease X time + neurodegeneration X time.

Amyloid + Vascular + Neurodegeneration		Within Race/Ethnicity		
		Non-Hispanic White	Non-Hispanic Black	Hispanic
Language	Time	0.02 [-0.02,0.05] p=0.38	-0.03 [-0.07,-1E-3] p=0.05	-0.06 [-0.12,6E-3] p=0.08
	Amyloid SUVR x Time	0.05 [-0.06,0.15] p=0.41	-0.07 [-0.13,-3E-3] p=0.05	-0.15 [-0.28,-0.01] p=0.04
	White Matter Hyperintensity x Time	-9E-3 [-0.05,0.03] p=0.65	-0.04 [-0.07,-0.01] p=0.01	0.02 [-0.05,0.09] p=0.66
	Cortical Thickness x Time	0.12 [-0.12,0.37] p=0.32	0.07 [-0.08,0.21] p=0.38	-0.11 [-0.51,0.28] p=0.58
Memory	Time	-0.06 [-0.13,-2E-3] p=0.06	-0.13 [-0.19,-0.07] p=1E-4	-0.05 [-0.12,0.03] p=0.26
	Amyloid SUVR x Time	-0.23 [-0.42,-0.04] p=0.03	-0.09 [-0.21,0.02] p=0.12	-0.16 [-0.31,1E-3] p=0.07
	White Matter Hyperintensity x Time	-0.03 [-0.09,0.04] p=0.42	-0.05 [-0.1,4E-3] p=0.08	0.09 [7E-3,0.18] p=0.05
	Cortical Thickness x Time	0.29 [-0.11,0.69] p=0.16	-0.15 [-0.41,0.11] p=0.27	-0.15 [-0.57,0.26] p=0.48
Processing Speed/ Executive Function	Time	-6E-3 [-0.09,0.08] p=0.9	-0.2 [-0.28,-0.12] p=3E-5	-0.07 [-0.17,0.03] p=0.18
	Amyloid SUVR x Time	0.2 [-0.06,0.46] p=0.15	-0.09 [-0.25,0.07] p=0.26	-0.19 [-0.44,0.06] p=0.15
	White Matter Hyperintensity x Time	-0.05 [-0.14,0.04] p=0.32	-0.11 [-0.19,-0.03] p=1E-2	-0.05 [-0.17,0.06] p=0.38
	Cortical Thickness x Time	-0.02 [-0.59,0.56] p=0.96	-0.72 [-1.07,-0.36] p=3E-4	0.03 [-0.55,0.6] p=0.93
Visuospatial ability	Time	-0.02 [-0.08,0.04] p=0.45	-1E-2 [-0.05,0.03] p=0.66	-0.08 [-0.16,-5E-3] p=0.05
	Amyloid SUVR x Time	-0.13 [-0.32,0.06] p=0.18	2E-3 [-0.07,0.08] p=0.96	-0.17 [-0.34,-5E-3] p=0.06
	White Matter Hyperintensity x Time	-2E-3 [-0.07,0.06] p=0.95	-0.05 [-0.09,-0.02] p=5E-3	0.01 [-0.08,0.1] p=0.79
	Cortical Thickness x Time	0.17 [-0.2,0.54] p=0.36	-0.1 [-0.29,0.08] p=0.27	5E-3 [-0.44,0.45] p=0.98

mechanisms for race/ethnicity differences in levels of AD-related biomarkers and their relationships with relevant clinical outcomes.

Second, we examined the relative contributions of amyloid, cerebrovascular disease, and neurodegeneration to cognitive decline over time within three major racial/ethnic groups. It is important to recognize that cognitive decline can only be attributed to a given pathologic driver if it is included in the model; otherwise, cognitive decline may be falsely attributed in single or incomplete biomarker models. Previous imaging studies investigated the singular or partial effects of cerebrovascular (Lao and Brickman, 2018; Rizvi et al., 2018; Stavitsky et al., 2010; Tosto et al., 2014; Windham et al., 2019; Wright et al., 2008) and/or traditional AD biomarkers (Aschenbrenner et al., 2018; Betthauser et al., 2020; Bilgel et al., 2018; Farrell et al., 2018; Farrell et al., 2017; Hanseeuw et al., 2019; Knopman et al., 2019; Kreisl et al., 2021; Landau et al., 2012; Scholl et al., 2016; Sperling et al., 2019) on

Table 4
Association parameters for the AV(N) model including amyloid, presence of infarct, and cortical thickness in each racial /ethnic group, focusing on slope parameters. Example model specification is as follows: Cognitive performance over time ~ intercept + time + age + sex/gender + education + *APOE ε4* + amyloid + cerebrovascular disease + neurodegeneration + age X time + sex/gender X time + education X time + *APOE ε4* X time + amyloid X time + cerebrovascular disease X time + neurodegeneration X time.

Amyloid + Vascular + Neurodegeneration		Within Race/Ethnicity		
		Non-Hispanic White	Non-Hispanic Black	Hispanic
Language	Time	0.02 [-0.02,0.06] p=0.23	-0.03 [-0.08,0.02] p=0.28	-0.07 [-0.15,0.02] p=0.12
	Amyloid SUVR x Time	0.04 [-0.06,0.15] p=0.4	-0.05 [-0.11,0.02] p=0.17	-0.15 [-0.29,-0.01] p=0.04
	Infarct x Time	-0.01 [-0.05,0.03] p=0.55	-0.01 [-0.05,0.03] p=0.54	7E-3 [-0.06,0.08] p=0.85
	Cortical Thickness x Time	0.12 [-0.12,0.36] p=0.32	0.11 [-0.05,0.27] p=0.19	-0.1 [-0.49,0.29] p=0.62
Memory	Time	-0.05 [-0.13,0.02] p=0.17	-0.12 [-0.21,-0.04] p=8E-3	-0.11 [-0.2,-0.02] p=0.03
	Amyloid SUVR x Time	-0.25 [-0.44,-0.07] p=0.02	-0.08 [-0.19,0.04] p=0.21	-0.15 [-0.32,0.01] p=0.09
	Infarct x Time	-0.02 [-0.09,0.05] p=0.61	-0.01 [-0.08,0.06] p=0.75	0.06 [-0.02,0.14] p=0.18
	Cortical Thickness x Time	0.31 [-0.09,0.72] p=0.14	-0.11 [-0.39,0.18] p=0.46	-0.12 [-0.56,0.31] p=0.58
Processing Speed/ Executive Function	Time	0.05 [-0.04,0.13] p=0.3	-0.16 [-0.29,-0.04] p=0.02	-7E-3 [-0.14,0.13] p=0.92
	Amyloid SUVR x Time	0.16 [-0.07,0.39] p=0.18	-0.04 [-0.22,0.13] p=0.63	-0.2 [-0.45,0.06] p=0.13
	Infarct x Time	-0.09 [-0.18,-4E-3] p=0.04	-0.04 [-0.14,0.06] p=0.47	-0.07 [-0.18,0.05] p=0.25
	Cortical Thickness x Time	-0.06 [-0.59,0.47] p=0.82	-0.63 [-1.05,-0.22] p=5E-3	-0.03 [-0.58,0.52] p=0.92
Visuospatial ability	Time	-0.03 [-0.1,0.04] p=0.47	-0.03 [-0.09,0.04] p=0.41	-0.06 [-0.16,0.03] p=0.19
	Amyloid SUVR x Time	-0.14 [-0.32,0.04] p=0.15	0.03 [-0.06,0.11] p=0.55	-0.17 [-0.34,2E-4] p=0.07
	Infarct x Time	7E-3 [-0.06,0.07] p=0.83	0.02 [-0.03,0.07] p=0.38	-0.03 [-0.11,0.05] p=0.43
	Cortical Thickness x Time	0.18 [-0.19,0.55] p=0.34	-0.11 [-0.32,0.1] p=0.33	8E-3 [-0.43,0.45] p=0.97

cognitive trajectory and generally demonstrate that individuals with indicators of greater pathophysiology, particularly those with higher levels of multiple pathophysiologies, show faster decline in cognition for samples of primarily Non–Hispanic White participants. There are few imaging studies investigating biomarker profiles across race/ethnicity to understand if cerebrovascular and AD pathways are consistent or have different relative contributions based on the degree to which they are present in each group.

In an amyloid-only model using longitudinal WHICAP data (Gu et al., 2015), faster multidomain cognitive decline was attributed to higher amyloid burden whereas in a vascular and neurodegeneration model using cross-sectional WHICAP data (Zahodne et al., 2015), lower multidomain cognitive performance

Table 5
Association parameters for the AV(N) model including amyloid, white matter hyperintensity volume, and relative hippocampal volume in each racial/ethnic group, focusing on slope parameters. Example model specification is as follows: Cognitive performance over time ~ intercept + time + age + sex/gender + education + *APOE ε4* + amyloid + cerebrovascular disease + neurodegeneration + age X time + sex/gender X time + education X time + *APOE ε4* X time + amyloid X time + cerebrovascular disease X time + neurodegeneration X time.

Amyloid + Vascular + Neurodegeneration		Within Race/Ethnicity		
		Non-Hispanic White	Non-Hispanic Black	Hispanic
Language	Time	5E-3 [-0.03,0.04] p=0.75	-0.04 [-0.07,-9E-3] p=0.02	-0.06 [-0.12,0.01] p=0.11
	Amyloid SUVR x Time	0.03 [-0.09,0.14] p=0.63	-0.06 [-0.11,-2E-6] p=0.06	-0.15 [-0.29,-0.02] p=0.03
	White Matter Hyperintensity x Time	-0.01 [-0.05,0.03] p=0.55	-0.04 [-0.07,-0.01] p=6E-3	0.01 [-0.06,0.08] p=0.74
	Hippocampal Volume x Time	-0.01 [-0.21,0.18] p=0.91	0.13 [-0.02,0.29] p=0.09	0.05 [-0.32,0.41] p=0.81
Memory	Time	-0.08 [-0.14,-0.03] p=6E-3	-0.12 [-0.18,-0.07] p=1E-4	-0.05 [-0.13,0.03] p=0.25
	Amyloid SUVR x Time	-0.25 [-0.44,-0.05] p=0.02	-0.1 [-0.21,0.01] p=0.09	-0.16 [-0.32,-4E-3] p=0.06
	White Matter Hyperintensity x Time	-0.04 [-0.1,0.03] p=0.27	-0.04 [-0.09,6E-3] p=0.09	0.09 [4E-3,0.17] p=0.05
	Hippocampal Volume x Time	0.04 [-0.29,0.37] p=0.8	0.21 [-0.08,0.49] p=0.17	0.02 [-0.37,0.4] p=0.93
Processing Speed/ Executive Function	Time	-5E-3 [-0.08,0.07] p=0.91	-0.16 [-0.25,-0.06] p=3E-3	-0.08 [-0.19,0.03] p=0.15
	Amyloid SUVR x Time	0.2 [-0.08,0.48] p=0.17	-0.14 [-0.33,0.06] p=0.18	-0.2 [-0.46,0.06] p=0.13
	White Matter Hyperintensity x Time	-0.05 [-0.14,0.05] p=0.35	-0.1 [-0.2,-4E-3] p=0.05	-0.03 [-0.15,0.09] p=0.6
	Hippocampal Volume x Time	-7E-3 [-0.47,0.46] p=0.98	-0.21 [-0.71,0.29] p=0.42	-0.27 [-1.02,0.47] p=0.47
Visuospatial ability	Time	-0.04 [-0.09,0.02] p=0.22	-6E-3 [-0.05,0.04] p=0.78	-0.09 [-0.17,-7E-3] p=0.05
	Amyloid SUVR x Time	-0.13 [-0.33,0.06] p=0.2	-5E-3 [-0.08,0.07] p=0.9	-0.18 [-0.35,-9E-3] p=0.05
	White Matter Hyperintensity x Time	-9E-3 [-0.08,0.06] p=0.78	-0.05 [-0.09,-0.02] p=6E-3	0.01 [-0.07,0.1] p=0.77
	Hippocampal Volume x Time	0.08 [-0.25,0.41] p=0.64	-0.05 [-0.25,0.15] p=0.62	-0.08 [-0.49,0.32] p=0.7

was attributed to higher WMH burden. In our amyloid, vascular, and neurodegeneration model, we find that faster language decline in Non–Hispanic Black participants is attributable to higher WMH in addition to higher amyloid, whereas the faster processing speed/executive function and visuospatial ability declines are likely attributable to higher WMH rather than higher amyloid. Further, in the vascular and neurodegeneration model using cross-sectional WHICAP data (Zahodne et al., 2015), the relative contribution of traditional AD biomarkers (i.e., hippocampal volume) was greater in Non–Hispanic White participants compared to Hispanic participants because Hispanic participants had greater WMH volume than Non–Hispanic White participants in that subset. We found that hippocampal volume was not differentially related to cognitive decline over time across race/ethnicity groups (i.e.,

Table 6
Association parameters for the AV(N) model including amyloid, presence of infarct, and relative hippocampal volume in each racial /ethnic group, focusing on slope parameters. Example model specification is as follows: Cognitive performance over time ~ intercept + time + age + sex/gender + education + *APOE ε4* + amyloid + cerebrovascular disease + neurodegeneration + age X time + sex/gender X time + education X time + *APOE ε4* X time + amyloid X time + cerebrovascular disease X time + neurodegeneration X time.

Amyloid + Vascular + Neurodegeneration		Within Race/Ethnicity		
		Non-Hispanic White	Non-Hispanic Black	Hispanic
Language	Time	0.01 [-0.02,0.05] p=0.47	-0.04 [-0.08,3E-3] p=0.08	-0.07 [-0.15,0.02] p=0.12
	Amyloid SUVR x Time	0.02 [-0.08,0.12] p=0.68	-0.04 [-0.1,0.03] p=0.27	-0.15 [-0.29,-0.02] p=0.03
	Infarct x Time	-0.01 [-0.05,0.02] p=0.5	-5E-3 [-0.04,0.03] p=0.77	0.01 [-0.06,0.08] p=0.79
	Hippocampal Volume x Time	-0.05 [-0.23,0.13] p=0.59	0.14 [-0.03,0.3] p=0.12	0.06 [-0.31,0.44] p=0.75
Memory	Time	-0.07 [-0.14,-5E-3] p=0.06	-0.11 [-0.19,-0.03] p=9E-3	-0.11 [-0.2,-0.02] p=0.03
	Amyloid SUVR x Time	-0.3 [-0.48,-0.11] p=1E-2	-0.08 [-0.19,0.03] p=0.16	-0.15 [-0.32,0.02] p=0.1
	Infarct x Time	-0.03 [-0.1,0.05] p=0.49	-0.02 [-0.08,0.04] p=0.55	0.06 [-0.02,0.15] p=0.15
	Hippocampal Volume x Time	-0.02 [-0.35,0.32] p=0.93	0.18 [-0.11,0.47] p=0.24	0.12 [-0.29,0.53] p=0.57
Processing Speed/ Executive Function	Time	0.04 [-0.04,0.12] p=0.29	-0.09 [-0.22,0.04] p=0.17	-0.03 [-0.17,0.11] p=0.7
	Amyloid SUVR x Time	0.13 [-0.09,0.36] p=0.25	-0.08 [-0.27,0.12] p=0.45	-0.21 [-0.46,0.04] p=0.11
	Infarct x Time	-0.09 [-0.18,-5E-3] p=0.04	-0.08 [-0.18,0.03] p=0.15	-0.07 [-0.19,0.04] p=0.23
	Hippocampal Volume x Time	-0.17 [-0.56,0.22] p=0.39	-0.16 [-0.66,0.33] p=0.53	-0.36 [-1.07,0.35] p=0.33
Visuospatial ability	Time	-0.04 [-0.11,0.03] p=0.26	-0.02 [-0.07,0.04] p=0.55	-0.07 [-0.16,0.03] p=0.18
	Amyloid SUVR x Time	-0.15 [-0.33,0.03] p=0.13	0.02 [-0.06,0.1] p=0.67	-0.18 [-0.35,-1E-2] p=0.05
	Infarct x Time	8E-3 [-0.06,0.07] p=0.81	0.01 [-0.03,0.06] p=0.51	-0.04 [-0.12,0.04] p=0.36
	Hippocampal Volume x Time	0.06 [-0.27,0.38] p=0.73	-0.06 [-0.28,0.15] p=0.56	-0.13 [-0.55,0.28] p=0.53

significant in one group but not another) after accounting for amyloid and cerebrovascular disease, suggesting that traditional AD biomarkers such as hippocampal volume may operate similarly across racial/ethnic groups given the same conditions (e.g., little to no cerebrovascular disease). Importantly, theses analyses do not suggest that cerebrovascular disease does not have an effect on cognitive trajectories in Hispanic participants; rather, this PET subsample of Hispanic participants did not have as much cerebrovascular disease present compared to the larger MRI subsample of Hispanic participants. Further, our use of racial/ethnic self-identification groups as a proxy for the unequal distribution of resources and opportunities among groups (i.e., structural racism) does not suggest that cerebrovascular disease does not have an effect on cognitive trajectories in Non–Hispanic White participants;

rather, cerebrovascular disease contributes to cognitive decline when it is present, and it is often more present in minoritized groups. Future studies incorporating a tau biomarker can further our understanding of multidomain cognitive decline within groups.

In the larger MRI substudy of WHICAP, higher WMH was associated with lower cortical thickness cross-sectionally, which was in turn associated with worse global cognition and memory performance (Rizvi et al., 2018). Additionally, higher baseline WMH was associated with cortical thinning in AD-signature regions longitudinally (Rizvi et al., 2020). In Non–Hispanic Black participants who enrolled in the PET substudy, higher cortical thickness was unexpectedly associated with *faster* processing speed/executive function decline; however, at baseline, those with infarcts had higher cortical thickness (Supplemental Fig. 2). In Hispanic participants, higher WMH was unexpectedly associated with *slower* memory decline; however, at baseline, those with high WMH had high hippocampal volume (Supplemental Fig. 2). Given that infarcts represent large vessel disease and WMH represent small vessel disease, these two cerebrovascular disease biomarkers may have different temporal relationships with downstream neurodegeneration and cognitive decline. In Non–Hispanic Black participants, those with an infarct, but high cortical thickness at baseline may have developed downstream neurodegeneration (unmeasured beyond baseline) that manifested in faster cognitive decline (measured beyond baseline) within the follow up period; while in Hispanic participants, those with high WMH and high hippocampal volume at baseline may not have developed downstream neurodegeneration (i.e., a slower timecourse compared to infarcts) that did not manifest in faster cognitive decline within the follow up period. The differential results may be further biased by the different number of follow-up visits in the Non–Hispanic Black and Hispanic groups and the low number of participants with longer follow-up durations who may disproportionately influence the models. Alternatively, cortical thickness in AD signature regions did not compensate for infarcts in Non–Hispanic Black participants who showed subsequently faster processing speed/executive function decline, while hippocampal volume compensated for WMH in Hispanic participants who showed subsequently slower memory decline. It is also possible that in both cases, selection bias into the PET substudy may have favored participants who were resilient to immediate neurodegeneration following a cerebrovascular injury; beyond being younger and having more years of education, potentially unmeasured factors may have moderated the effect of cerebrovascular injury on cognitive decline. Longitudinal biomarker studies with the inclusion of AD and cerebrovascular disease and an emphasis on reserve and resilience pathways may provide further insight into trajectories of cognitive decline.

Sample size precluded the investigation of interaction terms among amyloid, neurodegeneration, and vascular biomarkers, but we were still able to investigate the additive contribution of each biomarker in an AV(N) framework using multiple V and (N) biomarkers. Additionally, for this exploratory characterization, we chose a statistically liberal approach by further describing associations up to $p < 0.10$ and did not apply multiple comparison corrections; future studies will be needed to confirm the presence of these AV(N) associations (e.g., greater amyloid and faster memory decline in Non–Hispanic Black and Hispanic groups, $0.05 < p < 0.10$), which are likely operating, in larger samples that can validate these complex models. Another limitation was the lack of tau biomarker information. Recent studies that incorporate tau biomarkers found an effect of tau pathology on cognition (Kreisl et al., 2021) that may be additive (i.e., an independent effect of tau pathology above amyloid (Sperling et al., 2019)) or synergistic (i.e., an interaction between tau pathology and amyloid on cognitive decline (Betthauser et al., 2020)). As we collect more biomarker data in this ongoing study, we will gain more insight into the mechanistic relationships among amyloid, tau, cerebrovascular disease, neurodegeneration, and cognitive impairment during the development and progression of AD within each race/ethnicity group. Recent work demonstrated that plasma-based biomarkers may work similarly well within racial/ethnic groups (Brickman et al., 2021) and support larger sample sizes in future studies. Even with these recruitment strategies, a single multiethnic community study may not fully capture the effects within racial/ethnic groups as race in place is equally important (e.g., structural inequalities differ by regional policies (Ford et al., 2010)). Further incorporating environmental and social factors may provide insight into mixed findings of additive versus synergistic effects between amyloid, tau, and cerebrovascular disease on various cognitive domains by understanding specific pathways that will be relevant for particular groups in particular settings. These limitations are offset by the strengths of the current analysis, including the prospective, longitudinal, multimodal investigation of amyloid, cerebrovascular, and neurodegenerative biomarkers on the change infour key cognitive domains over time in a racially/ethnically-, linguistically-, and educationally-diverse community-based sample of older adults.

Our study adds to the growing body of literature that implicates cerebrovascular disease as a contributor to, if not driver of, cognitive decline that is characteristic of clinical AD progression, especially in the context of certain social determinants of health. Converging evidence across autosomal dominant AD (Lee et al., 2016) and AD in adults with Down syndrome (Lao et al., 2019) suggests that cerebrovascular disease biomarkers emerge during AD progression, even in the absence of vascular risk factors. Therefore, cerebrovascular disease could be more closely linked to AD than previously thought, supporting the widespread application of ATV(N) biomarker models. Future studies should test specific mechanistic pathways using multiple biomarkers of disease and multiple domains of cognition measured at multiple timepoints across the disease course and life course. Importantly, studies investigating health disparities in AD and related dementias should incorporate biological, environmental, and social factors together.

Verification

We confirm that this work is performed in accord with ethical standards, is original, and has not been published elsewhere nor is it currently under consideration for publication elsewhere. This manuscript has been read and approved by all co-authors. The authors have no conflicts of interest to report. We hope that you share our enthusiasm about this paper and will consider it for publication in *Neurobiology of Aging*.

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Disclosure statement

The authors have no actual or potential conflicts of interest.

CRediT authorship contribution statement

Patrick J. Lao: Conceptualization, Methodology, Formal analysis, Data curation, Writing – review & editing, Visualization. **Amelia K. Boehme:** Methodology. **Clarissa Morales:** Software, Formal analysis. **Krystal K. Laing:** Software, Formal analysis. **Anthony Chesebro:** Software, Formal analysis. **Kay C. Igwe:** Software, Formal analysis. **Jose Gutierrez:** Formal analysis. **Yian Gu:** Conceptualization. **Yaakov Stern:** Conceptualization. **Nicole Schupf:** Conceptualization. **Jennifer J. Manly:** Conceptualization, Funding acquisition. **Richard Mayeux:** Conceptualization, Funding acquisition. **Adam M. Brickman:** Conceptualization, Funding acquisition, Supervision.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2022.05.004.

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